PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Improvements in Material for Causing Local Anaesthesia

We, ASTRA PHARMACEUTICAL PRODUCTS INC., a Corporation organized and existing under the laws of the State of New York, United States of America, of 7 1/2 Neponset Street, City of Worcester, State of Massachusetts, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

THIS INVENTION relates to materials useful in the topical administration of local anaesthetic agents, especially of the lidocaine type, and to their production and use.

Local anaesthetic agents are usually administered topically as by applying solutions of the local anaesthetic by means of cotton wads or compresses or special applicator devices, for instance to the mucous membranes of the oral cavity, nares, or female urethra. It is evident that such a mode of administration has the marked disadvantage of great difficulty in administering only the required amount of local anaesthetic. Overdosage with its untoward side-effects, or application in too small a quantity or inadequate concentration to produce the desired anaesthetizing effect, frequently cannot be avoided. The same difficulties arise when applying the local anaesthetic in ointment, cream, or jelly form.

Topical absorption of local anaesthetics from aqueous solutions or ointments through the skin or mucous membrane varies considerably. In fact many of the local anaesthetics in the usual concentrations are not significantly absorbed through the intact skin. It is likewise rather difficult, if not impossible, to localize the action of a local anaesthetic in solution or ointment so that only the desired specific areas is anaesthetized. It is therefore desirable to provide a topical dosage form which would permit higher concentrations of local anaesthetic agents to be incorporated than are present in the ordinary solution, ointment, or jelly preparations, and to confine such high concentrations to specific areas of the body for improved activity.

Local anaesthetic agents are also administered by injection of their aqueous or saline solutions into the area to be anaesthetized. Such injection method has also all the disadvantages of the known methods of topical administration, especially the difficulty in administering the required amount of the local anaesthetic agent. Furthermore, injections are painful and the injection needle may cause injury to the nerve if it accidentally punctures it. Injection is also contraindicated in hemophiliacs or in patients which are highly apprehensive to injection. Furthermore, injection may cause inflammation of the tissue and spreading of infection.

It is an object of the present invention to provide a dosage form suitable for topical application without injection, and satisfying the requirements summarised above, which is stable and storable, and in which the local anaesthetic agent is protected against the detrimental effect of oxygen and other agents affecting its local anaesthetic activity. In addition the dosage form of the invention eliminates any risk of breakage of glass ampoules, containers, or the like in which the local anaesthetic agent is kept before use.

In one aspect the invention comprises a sheet-like material of a water-soluble, film-forming compound or composition having incorporated therein a local anaesthetic agent, e.g. of the lidocaine type, held in solution, or at least in extremely fine or colloidal dispersion, throughout the film or sheet by the film-forming compound or composition itself. The film-forming compound or composition may act as a protective colloid, to permit application to the desired area of the skin or

[*Price 4s. 6d.*]

mucous membrane. The local anaesthetic film or sheet need not be anhydrous. However, it is preferred to have it in a substantially dry and/or coherent state or form.

Suitable water-soluble, film-forming compounds which may be used include the water-soluble cellulose ethers such as methyl cellulose, ethyl cellulose, hydroxylated alkyl cellulose ethers, alkali metal carboxy methyl cellulose, alkali metal cellulose sulphate; hydrophilic polyvinyl compounds such as polyvinyl pyrrolidine, water soluble copolymers of vinyl pyrrolidone with ethyl acrylate, styrene, vinyl acetate, and other copolymerizable monomers; polyvinyl alcohol, partially hydrolyzed polyvinyl acetate or copolymers of vinyl acetate and copolymerizable monomers such as acrylic acid, methacrylic acid, crotonic acid or their esters; allyl acetate; copolymers of methyl vinyl ether and maleic acid anhydride; polyvinyl phosphenates such as polyvinyl phosphonic acid; polyitaconic acid; polyvinyl carboxamides such as polyacrylamide, copolymers of styrene and maleic acid anhydride; copolymers of ethylene and maleic acid anhydrides; copolymers of acrylamides and acrylic acid; polyelectrolytes such as alginic acid and alginates, pectin and film-forming polyuronic acids and their alkali metal salts; polysaccharides such as zein and amylose; vegetable gums such as guar gum, tragacanth, locust bean gum, and others; and partially formaldehyde-hardened, but still water-soluble, gelatin. The water-soluble, film-forming materials obviously must not destroy the local anaesthetic activity of the local anaesthetic agent.

Although water-soluble film-forming compounds are preferably employed, the local anaesthetic agent may be bound covalently by way of functional groups to suitable film-forming polymers which are not of themselves water-soluble but which form water-soluble acid addition complexes with the local anaesthetic agent and/or other bases. For instance, local anesthetics of the acid amide type such as lidocaine (α - diethylamino - 2,6 - dimethyl acetanilide) and others combine with water-insoluble or water-swellable acid polyelectrolytes such as carboxy polymethylenes to form soluble acid addition salt-like polymers which, on contact with aqueous solutions or mucous membranes, are hydrolyzed and thus release the local anaesthetic agent.

Likewise, local anaesthetics of the ester type (which usually contain basic groups) such as procaine (the diethylamino ethyl ester of *p*-amino benzoic acid) may be covalently bound by their amino groups to suitable polyelectrolyte polymers, for instance polyacrylic acid and the like.

The water-soluble film may be laminated or covered with a water-insoluble, impermeable or resistant backing material to achieve certain desired effects. The insoluble backing or carrier may be of such compositions as plastic, cloth, metal foil or combinations thereof, and may be united to the water-soluble film by lamination, heat, adhesives, pressure, or other suitable mechanical procedures or by wet casting a suitable liquid film-forming composition on such water-insoluble backing so that adhesion is effected on drying. The insoluble backing material may be coated with a pressure sensitive adhesive which will adhere to the anesthetically active water-soluble film and provide or assist adhesion to skin or mucous membrane on the area surrounding the anaesthetic dosage. The presence of the insoluble backing may facilitate application, localization and even improvement of environmental stability of the water-soluble film. The film and backing may be united in other known ways.

To protect the local anaesthetic film or sheet against dust, finger-prints or other contamination, it may be covered by a readily removable and disposible sheet or coating of any type compatible with the film material and the local anaesthetic agent, such as tissue paper or the like.

The sheet-like material may be enclosed and if desired hermetically sealed, between two such layers of a gas- and water-impermeable material. The water-soluble local anaesthetic film may then be stored for a prolonged period of time without absorbing water or losing water or plasticizer, or undergoing oxidative degradation of the film-forming material involving depolymerization and/or increased polymerization, or loss in local anaesthetic activity due to evaporation or degradation. The resulting pouch pack is opened by cutting or by using a strippable seal, whereafter the water-soluble local anaesthetic film is placed on the desired area. The pouch pack may be composed in the case of a non-strippable seal of a laminate of a fluoro-halocarbon plastic material and polyethylene bonded to a laminate of a polyester plastic material, an aluminium foil, and a polyolefin plastic with the seal between the polyethylene layer and the polyolefin layer. Packages with a strippable seal may consist of a laminate composed of a fluoro-halocarbon plastic material, polyethylene, and polypropylene bonded to the polyolefine surface of a laminate composed of a polyolefin plastic, aluminium foil, and a polyester plastic. Other laminate materials may, of course, also be used.

To use such a three-layer structure, it is preferred to remove both outside layers before applying the water-soluble layer to the mucous membrane to be anaesthetized.

The invention permits the provision of sheets of plastic material which contain a predetermined amount of the local anaes-

thetic agent. The weight ratio of local anaesthetic agent to the actual film-forming material may vary considerably depending upon the type of material selected. In general, higher concentrations of local anaesthetic agent than are usually found in solution, ointment, cream, or jelly vehicles may be incorporated. The agent may be incorporated in these high concentrations in the more potent form, i.e. as the base, as well as in the form of acid addition salts. The weight ratio of local anaesthetic agent to film-forming material may be as high as 1 : 1, or even higher, depending on the properties of the carrier material and its film-forming cohesiveness. For instance, 6 sq.cm. of a methyl cellulose film of 0.13 mm. thick, which weighs about 0.09 g., may contain 24 mg. of lidocaine, and will slowly dissolve and release this amount over a considerable period of time. The rate of dissolution of the film and release of anaesthetic agent can be varied by variations in the composition of the film.

The sheet-like compositions of the invention thus have the following advantages over the compositions, preparations and other means of applying local anaesthetic agents known and used heretofore:

(a) The local anaesthetic agent can be applied in a predetermined dose, and in higher concentration per unit weight or volume than in conventional vehicles or by conventional means.

(b) The local anaesthetic agent can be administered in such a manner that the duration of anaesthesia can be varied and predetermined.

(c) The action of the local anaesthetic agent can be localized to specific areas without substantially affecting other areas of the body.

(d) Proper formulation of the carrier sheet-like material permits adjustment and control of the speed of release of the local anaesthetic agent.

(e) Certain local anaesthetic agents can be used in their basic forms, in place of their acid addition salts, thus assuring more effective anaesthesia.

The film or sheet-like device according to the present invention is readily sterilized and supplied to the physician or dentist in a sterilized package, thus eliminating cumbersome and time-consuming sterilization of the injection needle as required when applying the local anaesthetic agent by injection.

Other advantages of the new device according to the present invention have been pointed out hereinabove.

In general, application of an anaesthetic in the form of a water-soluble film has the advantage that the dosage can readily be controlled by choosing the size of the film used.

It is occasionally advisable to add to the sheet-like structure an agent which promotes its adhesion to the skin or mucous membranes. Suitable plasticizers or adhesives may be added for this purpose. Those sheets which include polyvinyl alcohols and water-soluble cellulose ethers, for example, are inherently adhesive and do not necessarily require addition of adhesive components or modifiers. Water-soluble plasticizers which are also capable of forming films have proved of special value. Polyvinyl pyrrolidones have proved to be especially suitable for modifying polyvinyl alcohol and like films.

The new sheet-like structures have proved to be of special value in dentistry. For instance, a film of a suitable size containing the local anaesthetic agent may be applied to the gum at the place where the pain occurs. If a composition is used which slowly releases the anaesthetic agent, it is possible to suppress the pain for a prolonged period of time. Likewise, when using fast-releasing preparations containing relatively high concentrations and large amounts of the local anaesthetic agent, it is possible to cause local anaesthesia sufficient to permit extraction of teeth or minor operations.

The new film or sheet-like material, for instance, causes satisfactory pulp anaesthesia when applied in the buccal fold and over the tooth, and has proved to be as effective as an injected local anaesthetic agent. It has not been possible to produce operative or clinical anaesthesia, such as pulp anaesthesia, by means of the known ointments, jellies, and like preparations.

The new material has been used for removing small tumour growths in the mouth cavity, and has the advantage over the injection method that it does not cause inflammation. It can, of course, also be used to perform biapsies of soft tissue and other minor operations.

A thin, adhesive film containing small amounts of the local anesthetic agent and capable of slowly releasing the same can be applied to artificial dentures before they are inserted into the mouth. The slow release of the local anaesthetic agent will suppress pain and irritation during the period of accommodation.

It is evident that the local anaesthetic materials of the invention will find many applications in medicine and surgery. When they contain sufficient of the local anaesthetic agent, they produce rapid and effective anaesthesia of the mucous membranes such as those of the lower genitourinary tract, the oral and nasal cavities, and the anorectal area. They are also effective when topically applied to the broken skin for pain, burns, and/or abrasions.

For instance, a film of a predetermined size and local anaesthetic content is applied

to the skin at a specific operative site, and so manipulated as to permit release of the local anaesthetic, as by moistening with water, with a solution of a wetting or penetrating agent, or with some other composition capable of dissolving the film and producing anaesthetic activity.

Materials which are water-soluble may be inserted into the vagina or the rectum so as to cause local anaesthesia and permit the performance of minor operations on said mucous membranes. The film is preferably of such a composition that it is completely dissolved by the secretions of the mucous membranes.

The film or sheet-like structure may be manufactured by any suitable method. The film may, for instance, be produced from the previously prepared mixture by spreading it on a flat, smooth, and preferably polished surface to a desired wet thickness, and heating the spread liquid, preferably with forced air circulation, to evaporate water or other solvent and form the desired film.

Spreading or casting can be effected by conventional casting or coating procedures, for instance, band casting, knife coating, roll coating, or spray coating. Doctor or coating knives or spreaders of varying cross-section shapes can be used, for instance straight blade, tapered blade, J-knife, and hollow knife, depending on the viscosity characteristics of the film-forming liquid.

The film can be spread or cast on both rigid and flexible surfaces, the latter being supported flat by suitable means. Surfaces of metal, such as stainless steel, glass, flexible or rigid plastic, papers with or without previous surface coatings, or combinations of these materials, can be employed.

In one suitable procedure for making a film, the film-forming liquid is poured onto a glass plate and brought to the required thickness by spreading uniformly with a doctor blade; the plate is then heated in a circulating warm air oven at 90°C. until a dry film is obtained. Considerable latitude in temperature and air flow rate is admissible, but it is desirable to maintain the temperature below 100°C. to avoid too rapid evaporation. When cool, the dried film can be lifted from the plate and converted to pieces of the desired size and shape.

In another procedure a suitable film casting machine may be used. The usual casting procedures are employed, except that with water as the predominant solvent somewhat longer drying times are used. Approximately 0.1% of a suitable wetting agent added to the casting mixture facilitates removal from the belt or wheel when the film is made on a continuous basis.

In another procedure a single glass or polished stainless steel surface, approximately 12 inches wide and 8 feet long, is mounted in an oven heated with steam coils, electricity or other suitable means and the heated air circulated by a fan or blower to exhaust evaporating solvent. The oven is constructed with a hinged top to facilitate access to the casting surface, and closing during the drying cycle. An adjustable doctor blade approximately 9 inches wide is mounted on parallel guide bars or rods to facilitate uniform spreading of the liquid along the length of the plate. A reservoir at the terminal end of the plate permits recovery of excess liquid. After the liquid has been spread, the cover is closed and the film dried until it has the desired physical characteristics. The dried film is then cooled, removed from the plate and converted to pieces of the desired size and shape.

In a procedure for preparing a film on a paper backing, whether as a permanent support for the film or for subsequent stripping followed by rewinding of the unsupported film, a knife coater is used. One such machine has a tapered doctor blade, 20 inches wide and 5/16 inch thick at the coating surface, with guides 19 inches apart to control the width of the layer of the solution deposited on the paper. The blade is mounted over a mechanically driven rubber roll 24 inches wide and 12 inches in diameter, which both drives and supports the paper during the coating. The speed of rotation of the roll and the height and angle of the blade over the roll are adjustable. The paper is fed from a roll 20 inches wide through a drying chamber 22 feet long, in which the temperature is maintained at 90°C. and air is circulated by a fan or blower to remove evaporating solvent. During travel through the chamber, the paper is supported on ball bearing-mounted stainless steel rollers 24 inches apart at centres. The rate of travel of the paper through the machine is such that the water content of the coated film is reduced to approximately 2 percent. After leaving the drying chamber, the coated paper is picked up on a mechanical festoon unit, 5 feet long, for cooling. From the festoon, the coloured paper is rewound under light tension, preferably with interleaved glassine or other non-adherent paper. The coated paper is trimmed with slitting knives to a width of 18 inches to eliminate edges of variable thickness during the rewinding process. If coating is performed on release paper, the dried and cooled film is mechanically separated and rewound interleaved with non-adherent paper.

In another procedure for preparing a film, the film-forming material is compounded with suitable plasticizers and the local anaesthetic agent and the mixture extruded as a thermoplastic by means of thermoplastic extrusion equipment.

Films can also be formed on release or

adhesive coated papers, cloth, films or other structures by coating on paper or cloth coating machine or by modification of procedures previously cited.

The following Examples, in which the percentages are by weight, illustrate the invention.

EXAMPLE 1

Lidocaine hydrochloride	20 g.
Polyvinyl alcohol as sold under the trademark "Lemol 5-88"	20 g.
Sorbitol 70% (as plasticizer)	4 g.
Water	100 ml.

The mixture was cast on glass and dried at 105°C. for 5 minutes, after which the film was allowed to cool and stabilize at room temperature and humidity. This formula gave a clear, shining film, somewhat tacky, and very adherent to itself while warm, but which after cooling showed crystallization of the lidocaine salt in very fine dispersion. After crystallization, the film was no longer tacky. The final dry composition was:

Lidocaine hydrochloride	46.5%
Polyvinyl Alcohol	46.5%
Sorbitol	7.0%

EXAMPLE 2

Lidocaine base	10 g.
Ethanol	10 g.
Polyvinyl alcohol "Lemol 5-88"	20 g.
Sorbitol 70% (as plasticizer)	4 g.
Water	100 ml.

The base was dissolved in ethanol. The ethanol solution was added to the aqueous dispersion of polyvinyl alcohol and sorbitol. The mixture was cast, dried, and cooled, yielding a good, strong, almost transparent film in which the lidocaine base was uniformly and finely distributed. The final composition of the film was:

Lidocaine	30.5%
Polyvinyl alcohol	61.0%
Sorbitol	8.5%

The film was between 0.08 and 0.10 mm. thick.

EXAMPLE 3

A film is cast from the following mixture:

Methyl cellulose sold under the trademark "Methocel 60 MG" 50 cps	20%
Lidocaine base	10%
Propylene glycol	4%
Gelatin	2%
Ethanol 95%	20%
Water	54%

EXAMPLE 4

A film is cast from the following mixture:

Methyl cellulose sold under the trademark "Methocel 60 MG" 50 cps	20%
Tragacanth	5%
Lidocaine base	10%
Ethanol 95%	10%
Sorbitol 70%	5%
Propylene glycol	2%
Water	48%

EXAMPLE 5

A film is cast from the following mixture:

Hydroxyethyl cellulose sold under the trademark "Cellosize QP 15000"	10%
Lidocaine base	10%
Ethanol 95%	10%
Water	70%

EXAMPLE 6

A film is cast from the following mixture:

Amylose	16%
Propylene glycol	7%
Lidocaine base	5%
Butanol	4%
Water	68%

EXAMPLE 7

A film is cast from the following mixture:

Cellulose ether sold under the trademark "Klucel L"	15%
Propylene glycol	15%
Ethanol 95%	60%
Lidocaine base	10%

EXAMPLE 8

A film is cast from the following mixture:

Sodium carboxymethyl cellulose	11.5%
Sorbitol 70%	10 %
Propylene glycol	10 %
Gelatin	2 %
Lidocaine base	10 %
Ethanol 100%	10 %
Water	46.5%

EXAMPLE 9

A film is cast from the following mixture:

Sodium Alginate 2.5% Mucilage	75%
Propylene glycol	5%
Lidocaine base	10%
Ethanol 100%	10%

EXAMPLE 10

A film is cast from the following mixture:

Pharmaceutical grade polyvinyl pyrrolidone	12%
Lidocaine base	10%
Propylene glycol	2%
Ethanol 95%	28%
Polyethylene glycol 400	2%
Distilled acetylated monoglycerides sold under the trademark "Myvacet 9-40"	5%
Sorbitol 70%	2%
Water	39%

EXAMPLE 11

A film is cast from the following mixture:

Amylopectin	15%
Lidocaine base	10%
Glycerol	5%
Ethanol 95%	15%
Gelatin	2%
Propylene glycol	2%
Water	51%

EXAMPLE 12

A film is cast from the following mixture:

Methyl cellulose sold under the trademark "Methocel 4000"	10%
Lidocaine base	40%
Methylene chloride	25%
Chloroform	25%

EXAMPLE 13

A film is cast from the following mixture:

Polyvinyl alcohol	14.0%
Polyvinyl pyrrolidone	3.5%
Lidocaine base	14.0%
Carboxy - polymethylene sold under the trademark "Carbopol 934" mucilage 3%	14.0%
Sorbitol	3.5%
Propylene glycol	3.5%
Sucaryl	0.7%
Saccharin Sodium	0.7%
Flavouring agent	0.7%
Water	31.4%
Ethanol 95%	14.0%

EXAMPLE 14

Especially valuable films are produced by using polyvinyl alcohol as the film-forming material and polyvinyl pyrrolidone as a film-forming plasticizer. Such films can be cast from dispersions composed as follows:

Polyvinyl alcohol	10—20 %
Polyvinyl pyrrolidone	5—20 %
Lidocaine base or Lidocaine hydrochloride	2—40 %
Synthetic sweetening agent	0— 1 %
Flavouring agent	0— 0.2%
Colouring agent	0— 0.6%
Water	Balance to 100 %

Films prepared in this manner and cast to a dried thickness of 0.1 mm. to 0.5 mm. contain 10% to 50% by weight of lidocaine base, and 2.0 mg. to 8.0 mg. of lidocaine base per sq.cm.

Other film-forming materials and/or plasticizers which may be used in place of or in addition to the polyvinyl alcohol and/or polyvinyl pyrrolidone include:

Material	Amount present in film
Sorbitol 70%	0— 8 %
Gelatin	0— 2.5%
Colloidal magnesium aluminium silicate sold under the trademark "Veegum"	0— 1 %
3% Carboxy polymethylene mucilage sold under the trademark "Carbopol 934"	0—10 %
Distilled acetylated monoglycerides sold under the trademark "Myvacet 5-00"	0— 5 %
Distilled acetylated monoglycerides sold under the trademark "Myvacet 9-40"	0— 3 %
Arabinogalactan in a natural gum exudate as sold under the trademark "Stractan"	0— 1 %
Powdered vegetable colloid consisting of a mannogalactan from Cyamopsis tetragonoloba as sold under the trademark "Burtonite"	0— 0.2%
Polysaccharide gum of unknown chemical constitution as sold under the trademark "Kelzan"	0— 2 %
Potato Starch	0—15 %
Tragacanth	0— 1 %
Propylene glycol	0— 8 %
Glycerol	0— 2 %
Polyethylene oxide polymer sold under the trademark "Polyox"	0— 5.2%
Polyethylene glycol 300	0— 8 %

Surface active ingredients, emulsifiers, wetting agents, dispersing agents and other film additives such as the following products may also be added in the amount given:

Material	Amount present in film
Sorbitan mono - oleate - polyoxy - alkylene emulsifier sold under trademark "Tween 80"	0—2 %
Sodium lauryl sulphate	0—0.5%
Colloidal silica as sold under the trademark "Cab-O-Sil M5"	0—1 %

Of course, other suitable additives may be employed in place of those mentioned hereinabove, provided they do not substantially affect the cohesiveness of the film and the activity of the local anaesthetic agent.

In place of water as solvent, aqueous ethanol of concentration up to 30% can be used.

The preferred procedure of making such films as given in the preceding Examples is to disperse or dissolve the film-forming material and the plasticizer or modifier, for instance, polyvinyl alcohol and polyvinyl pyrrolidone, in distilled water while heating and stirring. The local anaesthetic agent is dissolved in a suitable organic solvent, preferably in ethanol and/or propylene glycol, when in the base form, or in distilled water when in the form of an acid addition salt.

The two solutions are then mixed with each other, with a high speed mixer; and if desired with sweetening, colouring, and/or

flavouring agents. The resulting mixture is then transferred to a high shear colloid mill and is milled until the mixture is smooth and free flowing.

The mixture is then cast on a polished surface, for instance to a wet thickness of about 0.65 mm., with a suitable coating knife or spreader, and is dried and cured at a temperature of 90°C. When using lidocaine base, which melts at this temperature, rapid cooling and controlled crystallization of the lidocaine is preferably effected under an external pressure as by a cooled roll or press.

The dried film has a thickness of about 0.5 mm., and may be cut to suitable size and packaged.

Example 15

3.0 kg. of methyl cellulose, 1.0 kg. of glycerol, and 100 kg. of water are intimately mixed, and the mixture is stirred at 65°C. until a clear colloidal solution is obtained. 1.0 kg. of lidocaine hydrochloride is added and dissolved. The solution is then cast in a thin layer onto the heated surface of a slowly revolving chromium-plated drum. The film casting machine is sealed and evaporation of the water to form the film takes place in the absence of air to safeguard against volatilization and/or oxidative destruction of the local anaesthetic. (Such destruction is of special significance with heat-sensitive local anaesthetic agents, for instance ester-type anaesthetics.) The dried film is about 0.5 mm. thick and is cut in pieces of the desired length which are then packed into polyethylene bags and sealed.

Example 16

5 kg. of sodium carboxymethyl cellulose, 0.5 kg. of glycerol, and 100 kg. of water are intimately mixed until complete solution is achieved. 1.0 kg. of lidocaine base is added and finely dispersed throughout the solution. The solution is then cast in a thin layer on a film casting machine under nitrogen, and dried to give a film of about 0.25 mm. thick. This is cut into pieces of the desired size which are packed and hermetically sealed in polyethylene bags.

Example 17

0.5 kg. of polyvinyl pyrrolidone are dissolved in 10 kg. of ethanol. 0.5 kg. of lidocaine base are added and the resulting mixture is cast on a film casting machine with the exclusion of air and is dried thereon to give a film about 0.2 mm thick. This is passed to another film casting machine, in which it is provided with a polyvinyl chloride backing layer 0.2 mm. thick.

Example 18

10 kg. of a 10% aqueous solution of polyvinyl alcohol of medium viscosity (degree of polymerization about 800) in which 0.5 kg. of the diethylamino-ethyl ester of *p*-aminobenzoic acid hydrochloride (procaine hydrochloride) have been dissolved is cast on a film casting machine in the absence of air to a film about 0.15 mm. thick, which is cut into pieces of the desired size. Each piece is provided with a pressure-sensitive adhesive tape of a size exceeding in at least two directions the size of the film pieces, so that the exposed parts of the adhesive tape can be used for fastening the film to the skin.

Example 19

10 kg. of a 20% aqueous solution of a vinyl alcohol-crotonic acid copolymer (95 : 5) obtained by saponification of the corresponding vinyl acetate-crotonic acid copolymer, are intimately mixed with 0.5 kg. of 2-dimethylamino ethyl-*p*-butylaminobenzoate. The solution is cast on a film-casting machine with the exclusion of air, and the resulting film is cut to pieces of the desired size and placed and sealed into polyethylene bags.

In place of the local anaesthetic agents used in the preceding Examples, there may be employed other local anaesthetic agents such as cocaine, α,β-eucaine, β - diethylamino - ethyl - 4 - amino benzoate, 2 - dimethylamino - ethyl - 4 - butylamino benzoate, 3 - (di - n - butylamino) - propyl - 4 - amino benzoate, diethylamino - neopentyl - 4 - amino benzoate, α,β - dimethyl - γ - dimethylamino - propyl - *p* - amino benzoate, β - n - amylamino - ethyl - *p*-amino benzoate, β - n - amylamino - ethyl - 3 - heptoxy - 5 - amino benzoate, 2 - diethylamino - 4 - methyl - pentyl - *p* - amino benzoate, 2 - isobutylamino - ethyl - *p*-amino benzoate, 2 - isobutylamino - ethyl - *m* - amino benzoate, 2 - methyl - 2 - propylamino - propyl - *p* - benzoate, 1 - cyclohexylamino - 2 - propyl benzoate, 3 - (2-methyl - 1 - piperidino) - propyl - 4 - cyclohexyloxy benzoate, 3 - (2 - methyl - 1-piperidino) - propyl benzoate, 2 - diethylamino - ethyl - 2 - chloro - 4 - amino benzoate, 2 - diethylamino - ethyl - 4-amino - 2 - propoxy benzoate, and other basic esters of 4-amino benzoic acid, 2-butoxy - N - (2 - diethylamino ethyl) - cinchoninamide, ω - butylamino - 2 - methyl-6 - chloro acetanilide, 3 - methyl - 2 - (diethylamino) - acetyl amino benzoic acid methyl ester, 2 - propylamino - 2′ - propionotoluidide, and other basic carboxylic acid amides, 4′ - butoxy - 3 - piperidinopropiophenone, 4 - [3 - (4 - butoxy - phenoxy) - propyl] - morpholine, N,N′ - bis-(4 - ethoxyphenyl) - acetamidine, 3 - piperidino - propylene dicarbanilate, 1 - butyl-2 - (2′,6′ - dimethyl - phenyl - carbamyl)-piperidine and other local anaesthetic agents.

It is also possible to provide a two-layer film of a water-soluble film-forming material,

in one layer of which the local anaesthetic agent is finely distributed, while the other layer is free thereof. In this manner it is possible to retard release of the local anaesthetic agent by saliva or other body fluids when applying the film with its layer containing the local anaesthetic agent to the mucous membrane to be anaesthetized.

The invention is further illustrated in the accompanying drawings, in which:—

Figure 1 shows the local anaesthetic activity of the following preparations:

(a) Ointment containing 5% of lidocaine base.
(b) Spray containing 10% thereof.
(c) Solution containing 5% thereof, and
(d) Placebo film according to this invention but without local anaesthetic agent.

Material applied and Method	Lidocaine base	Remaining on Tissue (though not necessarily at site of application)
A. 5% Lidocaine Ointment 1g. on "a-tip" held in buccal sulcus over upper premolars for 2 minutes	50 mg.	35 mg.
B. 5% Lidocaine Topical Solution 2 swabfuls rubbed on 2—1" strokes on attached gingiva over upper premolars	20 mg.	10 mg.
C. 10% Lidocaine Spray 2 metered doses on attached gingiva over upper premolars	20 mg.	
D. Lidocaine Film 1/2" × 1" strips on attached gingiva over upper premolars		
0 mg/cm²	0.0 mg.	
1 mg/cm²	3.0 mg.	
2 mg/cm²	6.0 mg.	
4 mg/cm²	12 mg.	
6 mg/cm²	18 mg.	

Specially designed cellulose sponge electrodes were incorporated into an individually constructed maxillary appliance. After determining DC resistance, a constant current was applied through these electrodes to the mucosa over the upper premolar.

A stimulation sensation threshold in microamps was then established on the left and right maxillary gingiva over the upper premolars. The appliance was then removed. Two of the eight products (randomly chosen) were then placed on the specified gingival area, one on the left and one on the right.

A 5 minute period was allowed to elapse before the next threshold was established. The appliance was returned to the mouth, the resistance was checked and the sensation threshold was again determined.

The above method was repeated at 5 minute intervals until the sensation threshold returned to its original level and clinical anaesthesia was no longer apparent. Clinical anaesthesia was determined by gentle stimulation of the gingiva with an explorer in the areas treated.

When both sides had returned to the original thresholds, two new products were tested.

The ointment and liquid preparations, of which quantities corresponding to about 50 mg. and 20 mg. respectively, of lidocaine base were applied, and the spray preparations of which a quantity corresponding to about 20 mg. of lidocaine base was applied, produced respectively threshold values not substantially exceeding about 0.53, 0.52 and 0.485 milliampers, corresponding to increases over the starting threshold value of 51.7%, 49.0% and 38.8%. The duration of the anaesthesia was between 21 minutes and 25 minutes.

In contrast thereto, the following threshold values and duration were observed with the film material of the present invention:

Figure 2 shows the local anaesthetic effect of the following film materials:

(e) Film strip containing 1 mg. of lidocaine.
(f) Film strip containing 2 mg. thereof.
(g) Film strip containing 4 mg. thereof, and
(h) Film strip containing 6 mg./cm² thereof.

The abscissas indicate at 0 the time on which the local anaesthetic preparation is applied and, as indicated by + numerals, the number of minutes after application.

The ordinates indicate the average threshold values, in milliamperes, to an electrical stimulus.

The above eight materials were tested by the procedure described below; each product was tested 4 times, twice on the left and twice on the right upper pre-molar gingival area:

Local anaesthetic agent per sq.cm.	applied	Maximum threshold value milliamp.	% increase	Maximum duration minutes
1 mg.	3 mg.	0.55	57.2	41 1/2
2 mg.	6 mg.	0.765	118	50
4 mg.	12 mg.	0.8	129	>50
6 mg.	18 mg.	0.805	130	>50

This table clearly illustrates the surprising results achieved by administration of the film preparations according to the present invention, which are not only more than twice as effective in doses that are about 1/9 to 1/3 the dose of the best known ointment preparation but in addition produce a local anaesthetic which is at least twice as prolonged as that of the known preparations. Even a dose of 3 mg. of lidocaine base, i.e. of about 1/17 to 1/19 the dose of the known ointment and liquid preparations, shows about the same increase in threshold value but a duration which is about twice as long as that of said known preparations.

This is believed to be due to the fact that the film permits not only better contact of the local anaesthetic agent and the mucous membrane, but also a higher concentration of the local anaesthetic agent on the area covered by the film, and thus avoids spreading of the local anaesthetic agent to the neighbouring areas which need not be anaesthetized, with resulting dilution of and reduction in the local anaesthetic activity.

WHAT WE CLAIM IS:—

1. A local anaesthetic material for topical application comprising a sheet-like structure of a film-forming material and, uniformly distributed throughout the structure, a local anaesthetic agent, said film-forming material being water-soluble and compatible with the local anaesthetic agent and, on dissolution, releasing the local anaesthetic agent for action at the site of application.

2. A local anaethetic material according to claim 1, wherein the film-forming material is an alkali metal carboxymethyl cellulose.

3. A local anaesthetic material according to claim 1, wherein the film-forming material is polyvinyl alcohol or polyvinyl pyrrolidone.

4. A local anaesthetic material according to any one of the preceding claims, wherein the local anaesthetic agent is a local anaesthetic compound of the acid amide type.

5. A local anaesthetic material according to claim 4, wherein the local anaesthetic agent is lidocaine base or lidocaine hydrochloride.

6. A local anaesthetic material according to any one of claims 1 to 3, wherein the local anaesthetic agent is of the ester type.

7. A local anaesthetic material according to any one of the preceding claims, wherein the sheet-like structure is combined with a supporting material which is less soluble in water than the film-forming material.

8. A local anaesthetic material according to any one of the preceding claims, wherein the sheet-like structure additionally contains an adhesive agent which assists adhesion of the sheet to the surface of a mocous membrane without substantially impairing absorption of the local anaesthetic compound from the sheet.

9. A local anaesthetic material according to any one of the preceding claims, wherein the sheet-like structure contains between 10% and 50% by weight of the local anaesthetic agent.

10. A local anaesthetic material according to any one of the preceding claims, wherein the sheet-like structure is not more than 0.5 mm. thick.

11. A local anaesthetic material according to claim 1 substantially as hereinbefore described.

12. A process for producing a local anaesthetic material claimed in any one of claims 1 to 11, which comprises forming a mixture of the local anaesthetic agent and the water-soluble film-forming material compatible therewith, and forming a sheet from the mixture.

13. A process according to claim 12 substantially as hereinbefore described.

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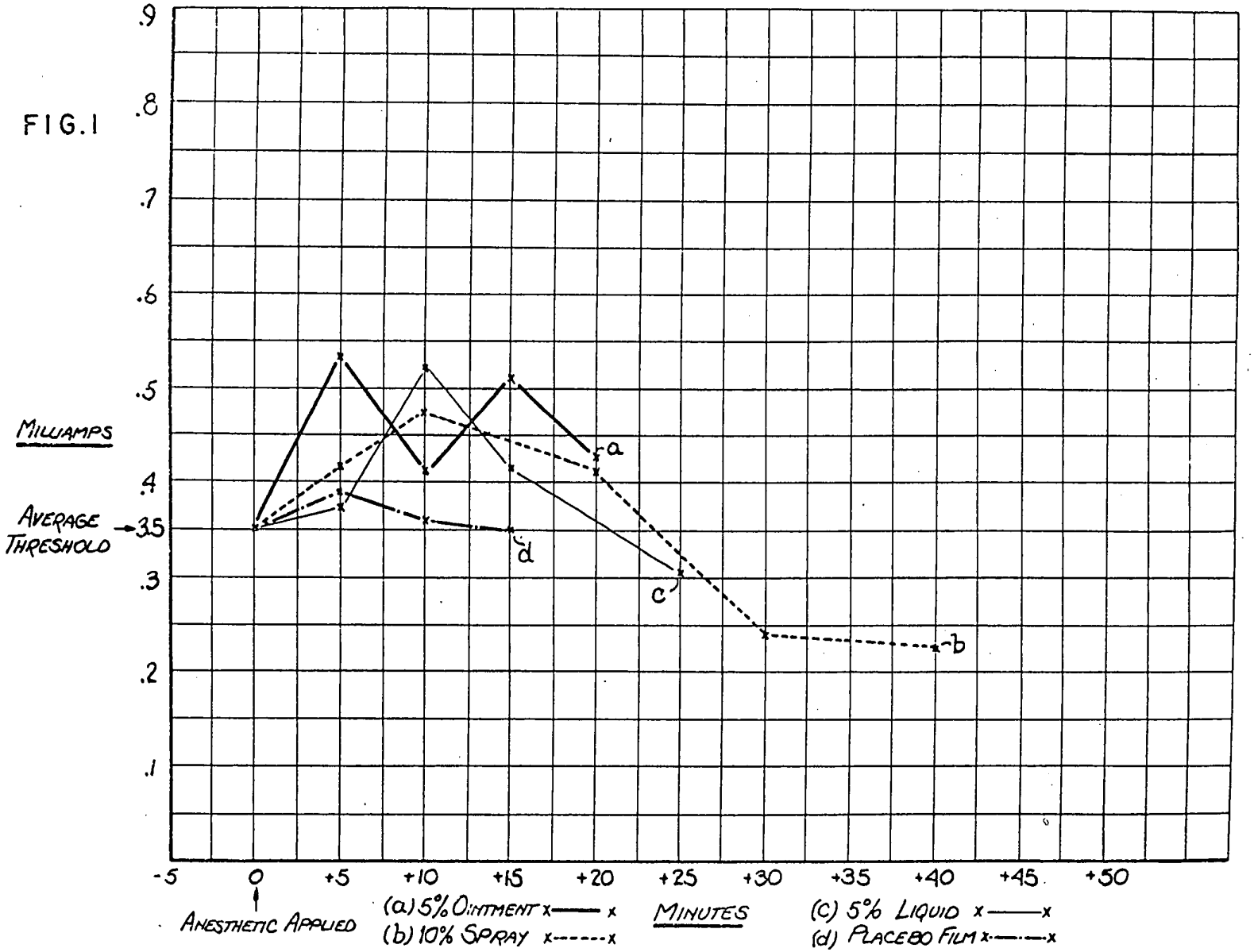
FIG. 1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MILLIAMPS
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-5
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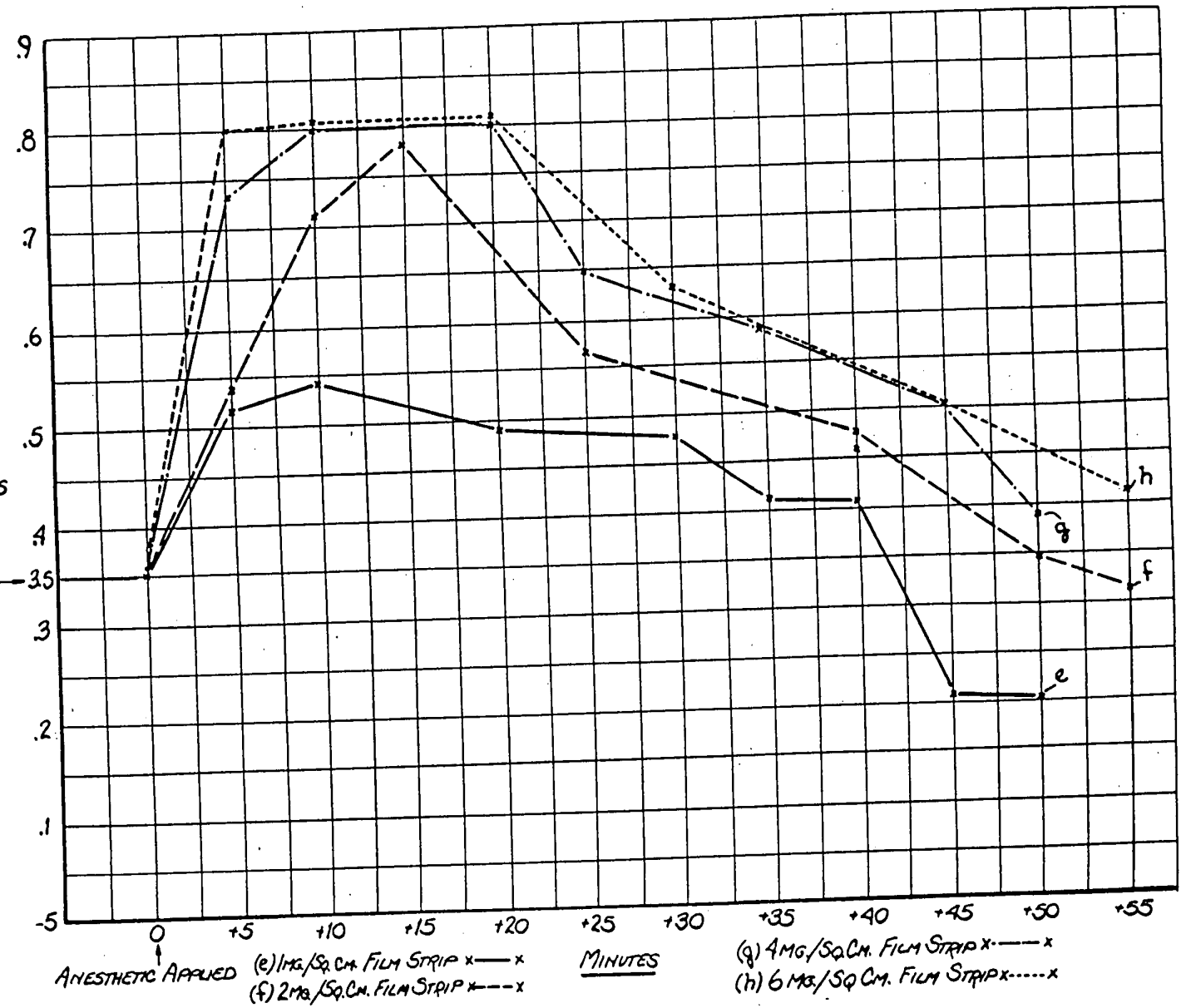
+30
+35
+40
+45
+50
ANESTHETIC APPLIED
MINUTES
(a) 5% OINTMENT x—— x
(b) 10% SPRAY x------x
(c) 5% LIQUID x—— x
(d) PLACEBO FILM x·—·—x

FIG. 2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.7
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MILLIAMPS
AVERAGE THRESHOLD
.35
0
+5
+10
+15
+20
+25
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+35
+40
+45
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+55
MINUTES
ANESTHETIC APPLIED
(e) 1 MG./SQ. CM. FILM STRIP x——x
(f) 2 MG./SQ. CM. FILM STRIP x– – –x
(g) 4 MG./SQ. CM. FILM STRIP x·——x
(h) 6 MG./SQ. CM. FILM STRIP x·····x
e
f
g
h

ERRATA

SPECIFICATION No. 1,108,837

Page 2, line 21, *for* "phosphenates" *read* "phosphonates"
Page 3, line 108, *for* "biapsies" *read* "biopsies"
Page 4, line 114, *for* "coloured" *read* "cooled"
Page 6, line 92, *for* "ingredients" *read* "agents"
Page 7, line 122, *for* "carbamyl" *read* "carbamoyl"
Page 9, lines 14 and 15, *after* "anaesthetic" *insert* "effect"
Page 9, line 18, *for* "1/19" *read* "1/9"
Page 9, line 43, *for* "anaethetic" *read* "anaesthetic"
Page 9, line 69, *for* "mocous" *read* "mucous"

THE PATENT OFFICE
24th February 1969

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